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Stereoselective Synthesis of Optically Active Di- and Trisubstituted Oxetanones as Chiral Dopants to Induce Ferroelectricity in Liquid Crystals

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Abstract. Optically active 3-hydroxybutyric and 3-hydroxyhexanoic acids were transformed into 3,4-disubstituted and 3,3,4-trisubstituted 2-oxetanones using two different approaches. Diastereoselective alkylation was performed either on dioxanone enolates or on lithoxy-lithium enolates. Some recently published unexpected results of alkylation of substituted dioxanones were used for the synthesis of a trisubstituted oxetanone.

Introduction

Since Meyer *et al.* [2] in 1975 first postulated and soon afterwards experimentally ferroelectricity in chiral liquid crystals, the so-called ferroelectric liquid crystals (FLC) are attracting great interest in both fundamental research and technological applications. The interest further increased, when Clark and Lagerwall [3] in 1980 demonstrated, that FLC's might be applicable for high-speed switching devices. To achieve short response times in FLC-displays a high spontaneous polarization and a low rotational viscosity at operating temperatures is required. The magnitude of spontaneous polarization depends on 1) the dipole moment perpendicular to the molecular longitudinal axis, 2) the distance between the chiral center, the lateral dipole, and the aromatic mesogenic core, 3) the restriction in free rotation in the region of the chiral center and the lateral dipole.

To fulfill these requirements, different concepts in designing FLC's were realized [4]. We use chiral heterocycles, in which the center of chirality and the lateral dipole is combined in a rigid core [5].

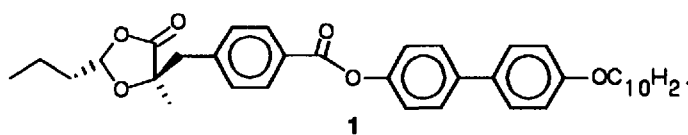
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Recently, we have synthesized the 1,3-dioxolan-4-one **1** as a new kind of substituted heterocycle with liquid crystalline and ferroelectric properties [6].

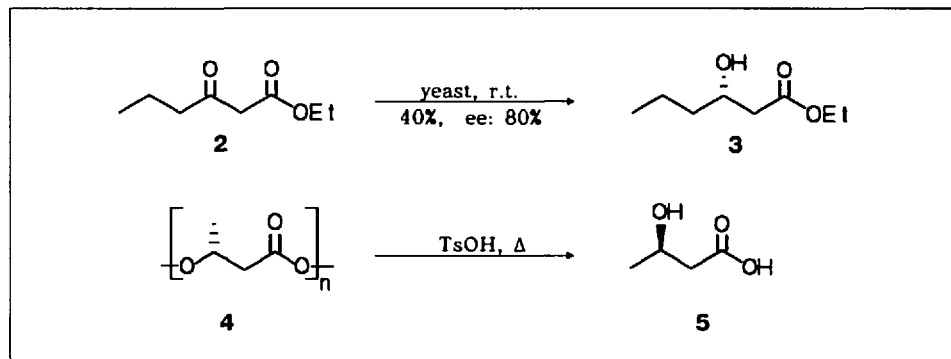
Results and Discussion

Now we report on the synthesis of 3,4-disubstituted and 3,3,4-trisubstituted 2-oxetanones, which seemed us to be superior to **1** because of their larger lateral dipole moment and higher rigidity. The required optically active α -mono- and α -disubstituted 3-hydroxycarboxylic acids were synthesized in two different ways. (3*S*)-Ethyl 3-hydroxyhexanoate (**3**) was prepared by yeast reduction [7] of commercially available ethyl 3-oxohexanoate (**2**). (3*R*)-Hydroxybutyric acid (**5**) was obtained by depolymerization of poly(hydroxybutyric acid) (PHB, **4**) with TsOH [8] (Scheme 1).

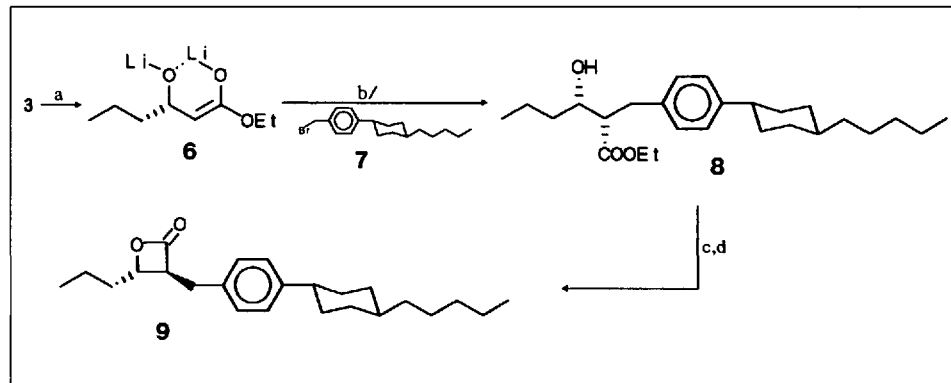
The ethyl ester **3** was alkylated with the benzylic bromide **7** [9] with high diastereoselectivity *via* the lithoxy-lithium



Scheme 1

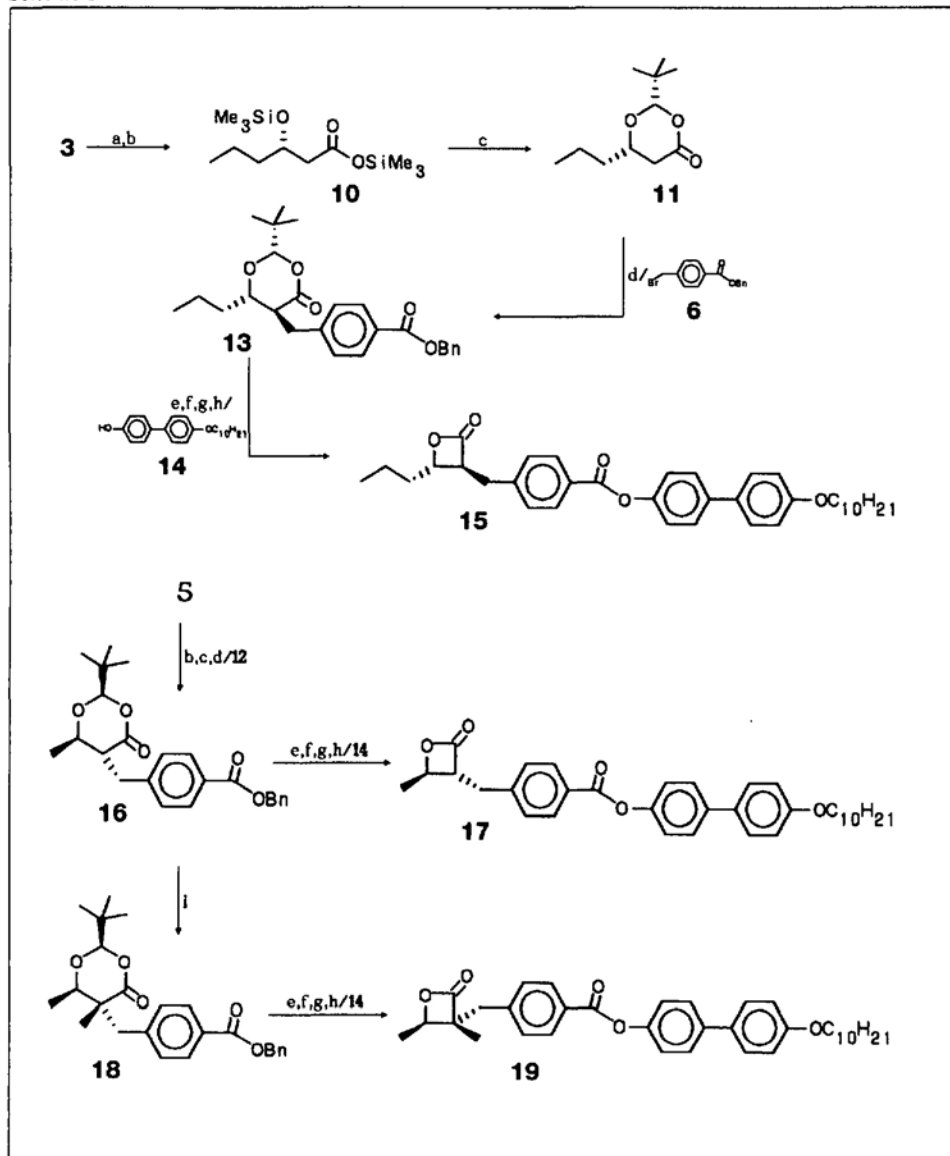


Scheme 2



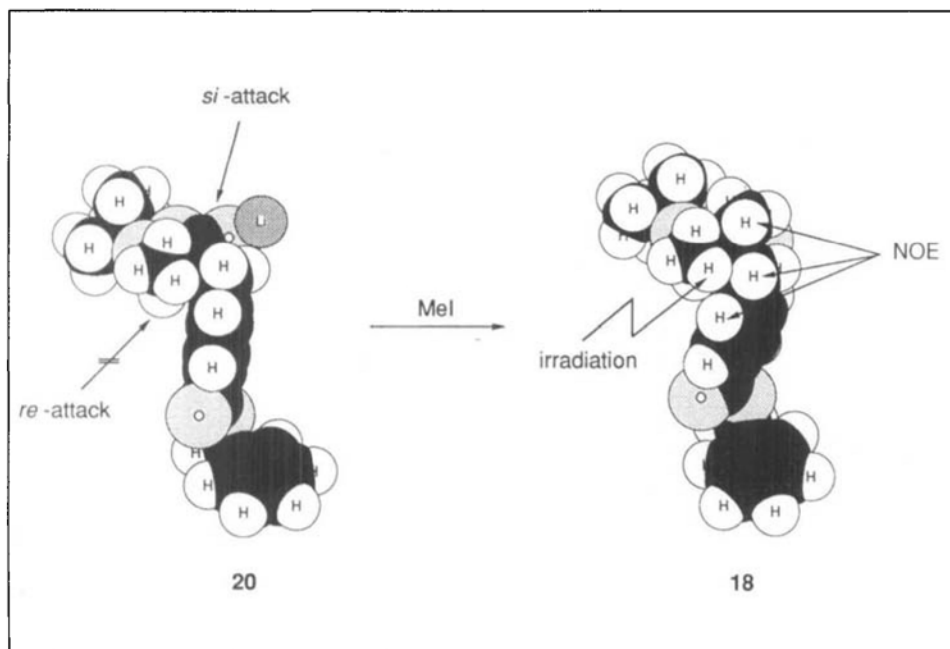
a) 2 equiv. LDA, LiCl, THF, 10 min, $-5^{\circ} \rightarrow -35^{\circ}$; b) 1 equiv. **7**, HMPA/THF 1 : 1, 2 h, $-35^{\circ} \rightarrow \text{r.t.}$, 40%; c) 2 equiv. KOH, EtOH, 18 h, r.t., 86%; d) 2 equiv. PhSO₂Cl, pyridine, 24 h, 4° , 82%.

Scheme 3



a) 2 equiv. KOH, EtOH, 24 h, r.t., 80–90%; b) 2 equiv. Et₃N, 2 equiv. TMSCl, CH₂Cl₂, 24 h, 0° → r.t., 94–9%; c) *t*-BuCHO, TMSOTf, CH₂Cl₂, 15 h, 78°, 90–96%; d) LDA, THF, 10 min, 78°, 12, 14 h, –78°, 55–60%; e) HCl, EtOH, SiO₂, r.t., 92–98%; f) 3 equiv. PhSO₂Cl, pyridine, 24 h, 4°, 70–78%; g) H₂, Pd/C (10%), EtOH, r.t., 93–97%; h) DCCI, DMAP, 14, CH₂Cl₂, 18 h, r.t., 70–79%; i) LDA, THF, 30 min, –78°, 4 equiv. CH₃I, 15 h, –78°, 25%.

Scheme 4



enolate **6** (Scheme 2). Only one diastereoisomer was observed in the NMR spectrum of the crude reaction product. Unlike the reported procedure [10a], the reaction has to be completed at r.t. in the presence of LiCl, if only 1 equiv. of the electrophile is used. At higher temperature (45°), we observed *retro*-aldol reaction of **8**. Saponification of **8** and cyclization with PhSO₂Cl [11] gave the oxetanone **9** [12] in 28% overall yield.

This oxetanone derivative has no liquid crystalline properties and is not useful as dopant in LC mixture M 89/85 [13], because it suppresses the desired S_C* phase. Therefore, we decided to use the same mesogenic substituent as in **1**.

This substituent could not be used directly as Br derivative for the benzylation step because of its insolubility in common solvents for alkylations like THF or Et₂O. So, we used the benzyl ester **12** of 4-(bromomethyl)benzoic acid [14]. With this electrophile, the benzylation of the lithoxy-lithium enolate **6** failed completely; stilbene was the usually observed main product. Therefore, we transformed (3*S*)-ethyl 3-hydroxyhexanoate (**3**) via the double trimethylsilylated derivative **10** into the corresponding dioxanone **11** [15] which could be benzylated in reasonable yields and, as reported [16], with high diastereoselectivity (Scheme 3). Ring opening of the labile dioxanone **13** [17] to the β-hydroxy acid and ring-closure to the oxetanone, hydrogenolysis of the benzyl ester and esterification of the benzoic acid with the hydroxy biphenyl ether **14** gave in good overall yield the oxetanone **15** which exhibits liquid crystalline properties (phases: Cr (115 N* 120.9 BP I 121.9 BP II 122.1) 135.9 I).

In the same manner, oxetanone **17** was prepared, starting from (3*R*)-3-hydroxybutyric acid **5**. The liquid crystalline properties of **17** are similar to **15**. For comparison of the physical properties of **15** and **17** with **1**, we synthesized the trisubstituted oxetanone **19** via alkylation of **16** with LDA/MeI. According to the recently published results of Seebach and Pietzonka [18] we expected an alkylation *cis* to the Me group at C(6), which would lead to the oxetanone **19** with the desired *trans*-configuration. In fact, NOE experiments performed at the oxetanone **19** [19] clearly show the *cis*-configuration of both Me groups. The *si*-attack of the electrophile on the enolate **20** was explained by the fact that the Me group at C(6) and the 1,3-allylic strain presses the aromatic ring of the benzylic group into the *re*-side of the enolate so that the *si*-attack of the electrophile now will be preferred [20]. Molecular modeling calculations [21] of the conformations of the enolate **20** and the diox-

anone **18** support this explanation (Scheme 4).

The calculated conformation of **18** also explains why irradiation on the Me group at C(6) causes an irritating NOE on both substituents at C(5) and on the *ortho*-H of the Ph group [22][23], because the Me group of C(6) has nearly the same distance to the Me and the CH₂ group at C(5) and to the *ortho*-H of the Ph group. Moreover, the calculated conformation in **18** explains, why irradiation on the Me group at C(5) causes a NOE only on the CH₂ group and not on the *ortho*-H of the Ph group.

Oxetanones **15** and **17** induce spontaneous polarization in smectic C liquid crystal hosts, when used as dopants [24]. The highest values of spontaneous polarization (>100 nC/cm², extrapolated) they induce, when the host S_C-material consists of the olefines, obtained by thermal cyclo-elimination of CO₂ from the corresponding oxetanones.

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- [12] M.p. 63°. [α]_D²⁰ = -12.2 (*c* = 1.20, CHCl₃). IR (CHCl₃): 2960s, 2930s, 2860s, 1820s, 1140m. ¹H-NMR (400 MHz, CDCl₃): 0.85 (*t*, *J* = 7, 3 H); 0.90 (*t*, *J* = 7, 3 H); 1.04 (*qd*, *J* = 12.5, 3, 2 H); 1.15-1.36 (*m*, 13 H); 1.59 (*dddd*, *J* = 14, 9.5, 6.2, 6, 1 H); 1.77 (*dddd*, *J* = 14, 9.5, 6.8, 6, 1 H); 1.83-1.90 (*m*, 4 H); 2.44 (*tt*, *J* = 12.5, 3, 1 H); 2.97 (*dd*, *J* = 14.5, 9, 1 H); 3.12 (*dd*, *J* = 14.5, 6, 1 H); 3.45 (*ddd*, *J* = 9, 6.8, 4, 1 H); 4.19 (*ddd*, *J* = 6.8, 6.2, 4, 1 H); 7.1/7.15 (*2m*, 4 H). MS (*m/z*, %): 356 (78, M⁺), 312 (100), 257 (30), 243 (21), 159 (70), 117 (93), 84 (99), 55 (99). HR-MS: *M* calc. for C₂₄H₃₆O₂: 356.2715; found: 356.2715.
- [13] M 89/85; Cr 10 S_C 84.5 S_A 93.5 N 105 I, available from Hoechst AG, Frankfurt am Main.
- [14] This bromide was obtained in two steps via α -bromination of *p*-toluic acid followed by esterification with PhCH₂OH/DCCI (46% overall yield) or alternatively via esterification of 4-formylbenzoic acid with PhCH₂OH/DCCI, followed by reduction of the formyl group with NaBH₄ in THF and bromination of the alcohol with PBr₃ in benzene (70% overall yield).
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- [19] M.p. 163°. [α]_D²⁰ = -12.3 (*c* = 1.00, CHCl₃). IR (KBr): 2930s, 2850s, 1810s, 1740s, 1615m, 1500m, 1475w, 1280s, 1210s, 1180m, 1085m, 1025w, 835m. ¹H-NMR (400 MHz, CDCl₃): 0.89 (*t*, *J* = 7, 3 H); 1.25-1.40 (*m*, 12H); 1.29 (*s*, 3H); 1.42 (*d*, *J* = 6.5, 3 H); 1.48 (*br. quint.*, *J* = 7, 2 H); 1.81 (*br. quint.*, *J* = 7, 2 H); 3.01, 3.21 (*AB*, *J*_{AB} = 14, 2 H); 4.00 (*t*, *J* = 7, 2 H); 4.60 (*q*, *J* = 6.5, 1 H); 7.0/7.5 (*2m*, 4 H); 7.25/7.6 (*2m*, 4 H); 7.35/8.2 (*2m*, 4 H). ¹H-NOE-NMR (400 MHz): irradiating the *q* at 4.60 causes NOE on *AB* system at 3.01 and 3.21 and on *ortho*-H at 7.35. MS (*m/z*, %): 542 (4, M⁺), 498 (22), 217 (8), 185 (5), 173 (100). HR-MS: *M* calc. for C₃₅H₄₂O₅: 542.3034; found: 542.3035.
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- [21] SYBYL Molecular Modeling Software Version 5.4, January 1991, Tripos Associates Inc. For the calculations the Tripos forcefield was used. The graphic was made with Chem 3Dplus. Calculations and graphics were made at the ETH-Zürich. The authors wish to thank Prof. Dr. D. Seebach for the possibility of calculating and printing the preferred conformations of enolate **20** and dioxanone **18**.
- [22] The NOE of the similar (2*R*,5*S*,6*R*)-5-benzyl-2-(*tert*-butyl)-5,6-dimethyl-1,3-dioxolan-4-one led first to the wrong assignment of configuration at C(5) of that dioxanone derivative (see [14b]) which would recently revised (see [18]).
- [23] [α]_D²⁰ = +59.0 (*c* = 1.37, CHCl₃). IR (CHCl₃): 2990s, 2970s, 2880s, 1720s, 1615m, 1490m, 1465m, 1390m, 1280s, 1125s, 955m. ¹H-NMR (400 MHz, CDCl₃): 0.89 (*s*, 9 H); 1.26 (*d*, *J* = 6.5, 3 H); 1.36 (*s*, 3H); 2.51, 3.64 (*AB*, *J*_{AB} = 14, 2 H); 3.65 (*q*, *J* = 6.5, 1 H); 4.60 (*s*, 1 H); 5.35 (*s*, 2 H); 7.3/7.9 (*2m*, 4 H), 7.32-7.47 (*m*, 5 H). ¹H-NOE-NMR (400 MHz): irradiating the *s* at 4.60 causes NOE on *q* at 3.65, irradiating the *d* at 1.26 causes NOE on *AB* system at 2.51 and 3.64, on *ortho*-H at 7.3 and on *s* at 1.36, irradiating the *s* at 1.36 causes NOE on *AB* system at 2.51 and 3.64 and on *d* at 1.26. MS (*m/z*, %): 410 (2.3, M⁺), 353 (5), 324 (19), 307 (40), 280 (8), 279 (4), 255 (5), 233 (12), 217 (19), 189 (8), 173 (52), 145 (11), 91 (100). HR-MS: *M* calc. for C₂₅H₃₀O₅: 410.2093; found: 410.2093.
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